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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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(54) Title: NOVEL ANTAGONISTS OF CXCR3-BINDING CXC CHEMOKINES

(57) Abstract: Novel antagonists of CXCR3-binding CXC chemokines, and in particular of human CXCL11, can be obtained by generating mutants of such chemokines in which the binding to glycosaminoglycans (GAGs) is impaired due to non-conservative substitutions of amino acids involved in this interaction. Compounds prepared in accordance with the present invention can be used to block the activity of CXCR3-binding CXC chemokines on CXCR3-expressing cells, thereby providing therapeutic compositions for use in the treatment or prevention of diseases related to excessive activated T cells migration, such as graft rejection and autoimmune diseases, and of diseases needing an increase of vascularization, such as ischemic heart disease.

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): PROUDFOOT,
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INTERNATIONAL SEARCH REPORT

International Application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/52 C07K19/00 C12N15/19 C12N15/62 A61K38/19
C12N5/06 C12N5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, EPO-Internal, BIOSIS, SEQUENCE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 739 103 A (ROLLINS ET AL.) 14 Apr 11 1998 (1998-04-14) column 2 -column 3; claims 1,3,8 ---	
A	US 2002/018776 A1 (HANCOCK) 14 February 2002 (2002-02-14) column 3; claims 8-10 ---	
A	US 6 140 064 A (MOSER BERNHARD ET AL) 31 October 2000 (2000-10-31) the whole document ---	
A	US 5 977 334 A (RANSOHOFF RICHARD ET AL) 2 November 1999 (1999-11-02) column 3; figure 1A ---	
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *G* document member of the same patent family

Date of the actual completion of the international search

14 January 2004

Date of mailing of the international search report

09/02/2004

Name and mailing address of the ISA

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Schmidt, Harald

INTERNATIONAL SEARCH REPORT

International Publication No
PCT/EP 03/50211

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02 43758 A (SCHERING CORP) 6 June 2002 (2002-06-06) claims 1-8 ---	
A	US 5 656 724 A (DALY THOMAS J ET AL) 12 August 1997 (1997-08-12) SEQ ID NO:7; column 3 -column 4; claims 1-6; figure 1 ---	
A	US 5 969 093 A (CARLIN MCKEOUGH ET AL) 19 October 1999 (1999-10-19) SEQ ID NO:9; column 10 ---	
A	WO 02 04015 A (BRADBURN JAMES A ;BOTTI PAOLO (US); CHEN SHIAH YUN (US); CRESSMAN) 17 January 2002 (2002-01-17) SEQ ID NO:24; page 6; claims 1-7; figure 10D ---	
A	LOETSCHER P ET AL.: "The Ligands of CXC Chemokine Receptor 3, I-TAC, Mig, and IP10, Are Natural Antagonists for CCR3" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 5, 2 February 2001 (2001-02-02), pages 2986-2991, XP002266874 the whole document -----	

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/50211

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 34 to 36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1,5-11,13-36 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,5-11,13-36 (all partially)

The scope of claims 13-36, in as far as the expressions "antagonists of claims 1 to 12 wherein one or more amino acids '...! have been '...! deleted", "mimetics", "active fractions", "precursors" and "derivatives" are concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to these expressions.

Moreover, present claims 1,5-11 and 13-36 relate to antagonists defined by reference to the sequence of human mature CXCL11.

1.) Mutants of CXCL9 are based on a substitution of at least one basic residue at positions 46,62,66 and 70 of human mature CXCL11. However, due to a gap in the sequence of CXCL9 at corresponding position 47, the numbering of the following residues of CXCL9 is unclear with regard to the basic residues to be substituted (see e.g. the two lysine residues at positions 65 and 66 of CXCL9 corresponding to positions 66 and 67 of human mature CXCL11).

2.) Mutants of human CXCL10 are additionally substituted at positions corresponding to residue numbers 74 and 75 of human mature CXCL11. However, since human mature CXCL11 has only 73 amino acid residues, this reference remains totally unclear.

The use of these references to human mature CXCL11 in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the positions the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Consequently, the search has been restricted to those parts of the claims relating to antagonists consisting of and comprising mutants of (1) CXCL11, (2) CXCL10 without the additional substitutions at positions 74 and 75, and (3) CXCL9 without the substitutions at positions 66 and 70.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Publication No

PCT/EP 03/50211

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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